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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/257,650	02/25/1999	MASAHIKO FUJINO	48194	2632
21874	7590	04/13/2006	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			SHAHER, SHULAMITH H	
			ART UNIT	PAPER NUMBER
			1647	
DATE MAILED: 04/13/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/257,650	FUJINO, MASAHIKO	
	<b>Examiner</b>	<b>Art Unit</b>	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 January 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 45-57 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 45-57 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **Detailed Action**

#### ***Status of Application, Amendments, And/Or Claims***

The amendment received 17 January 2006, in response to Office Action of 17 October 2005 has been entered. Claims 1-44 have been cancelled at Applicant's request. New claims 45-57 have been presented and entered. Claims 45-57 are under examination. The pertinent remarks/arguments filed with the amendment received 17 January 2006 will be responded to herein.

The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office actions.

Claims 18, 19, 22, 23, 28-33 and 35-44 have been cancelled. Therefore, rejections of claims 18, 19, 22, 23, 28-33 and 35-44 are rendered moot.

New issues are set forth below.

### **Maintained Rejections/New Grounds for Rejection**

#### ***35 U.S.C. § 112, Second Paragraph***

The rejection of claims 18, 19, 22, 23, 28-33 and 35-44 under 35 U.S.C. 112, second paragraph as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are now applied to claims 45-57 for reasons of record and those outlined below. The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

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Claims 45 and 46 recite methods using such terms as "substantially changed affinity" without clearly defining the boundaries of what is meant by the term. Applicant argues that the term is common and well known in the English language and provides a clear and definite meaning to one of ordinary skill in the art (page 5, last paragraph bridging page 6, first paragraph of Remarks, 17 January 2006). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Neither the specification nor the art have provided clear definitions of these terms. On page 16 applicant states "The term "substantial change" as used above means a change to the extent that a disease can be caused when the affinity of the natural ligand for the normal and aberrant receptors are compared: and may be any change, whether significant or insignificant, as long as it is capable of causing a disease." A "substantial change" cannot be defined as "any change, whether significant or insignificant". Applicant traverses the Examiner's rejection of claims over the use of terms "operational activity", "operates", and "operate in a manner similar to". Applicant asserts these terms are used in a similar manner in submitted abstracts of papers by Czyrak et al (2000, Brain Res Mol Brain Res 85:209-217), Kuzmin et al (2000, J Pharm Exp Ther. 295:1031-1042), Scislo et al (2000, Am J Physiol 278:H2057-2068) and Maritano et al. (2000, Oncogene 19:1354-61). These assertions have been fully considered but are not found to be persuasive for the following reasons. The term "operate" as used in the abstracts of Czyrak et al (2000, Brain Res Mol Brain Res 85:209-217), Kuzmin et al (2000, J Pharm Exp Ther. 295:1031-1042), Scislo et al (2000, Am J Physiol 278:H2057-2068) and Maritano et al. (2000, Oncogene 19:1354-61) are synonymous, in common usage, with the word "function". The terms "operational activity", "operates", "operate in a manner similar to" are not explicitly defined in the specification nor can these terms be read as synonymous with "functional activity" "functioning" or "functions" in light of the claims of the instant invention. It is unclear whether applicant intends the phrases to read as "activating" or "stimulating", therefore the rejection is maintained.

Claim 45(a) recites "expressing an aberrant genetic product". Claim 45(b) recites "the aberrant receptor obtained in (a)". An aberrant genetic product encompasses a

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broader range of proteins than just aberrant receptors. Therefore, there is insufficient antecedent basis for this limitation in the claim.

Claim 46 (d) recites "selecting an agonist or antagonist to the aberrant receptor". It is not clear at which step in the method of Claim 45 is step d is to be performed nor how it relates to steps a-c of claim 45.

Claim 47 recites "restoring normal function to a signal transduction system of a cell". However, the aberrant receptor in the independent claim (claim 45) has been identified as having changed affinity for the natural ligand with no recitation of abnormal functioning of signal transduction system. Furthermore, Claim 47 is an incomplete method claim. To be complete, a method claim must state a goal in the preamble of the claim, and conclude having achieved that goal. The goal recited in the preamble of Claim 47 is "restoring normal function to a signal transduction system of a cell"; however the method step recites "an activity that restores the normal function of the cell". It is not clear which function Applicant intends to restore.

Claims 47-49 each recite an additional step c; however, step c is also recited in the base claim, claim 45. It is not clear how the step c recited in claims 47-49 relate to the one recited in claim 45. Step c of claim 47 recites "assaying the activity of said substance on said receptor; step c of claims 48 and 49 recites "assaying the activity of said substance". It is not clear how the additional step c's further limit the method of claim 45.

Claim 48 recites "(c) assaying the activity of said substance on said product". It is not clear to what product step c refers.

Claims 48 and 49 both recite "preparing a substance". It is not clear how the substance is to be prepared, and at which step in the method of claim 45 the step of "preparing a substance" is to be done.

Claim 49 recites, in step c, "assaying the activity of said substance" and "preparing a substance". It is not clear if "said substance" and "a substance" refer to the same substance.

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Claim 50 recites the limitation of “an aberrant receptor prepared by expressing in a cell the gene encoding the aberrant receptor”. This fails to further limit the method, as there are no other commonly art-recognized means of preparing aberrant receptors.

Claim 51 is rejected as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph. Claim 51 is in a narrative form, and fails to recite method steps that would need to be performed to identify an aberrant receptor. The claim encompasses a method for screening substances in which “the gene encoding the aberrant receptor is an aberrant receptor encoding gene”. This is a circular statement and fails to further identify the gene. The claim further recites “gene specified by comparative analysis”; it is not clear how an aberrant receptor encoding gene is to be “specified”. Additionally, the claim recites “a gene prepared from a cell of a mammal....that does not carry the aberrant receptor”. The claim does not specify that this gene actually encode the wild-type receptor, and thus could mean any gene from a mammal. Applicant traverses the rejection that the term “a gene” is indefinite because it can specify any gene. Applicant’s arguments have been fully considered but are not found to be persuasive for the following reasons. Applicant states that invention “provides a general method of screening for modulators of aberrant proteins e.g., receptors” (page 6 of 11, 4<sup>th</sup> paragraph). Methods of screening for modulators of aberrant proteins are well known in the art. Aberrant proteins encompass many more types of proteins than just aberrant receptors. Therefore, without further definition, the term “a gene” is indeed vague and indefinite.

Claim 52 recites “separating the aberrant receptor”. There is no recitation of what the aberrant receptor is being separated from. There are no method steps disclosing isolation of the receptor. Furthermore, the claim recites “providing a substance with the aberrant receptor”. It is unclear whether the substance comprises, contains or encompasses the aberrant receptor or if the applicant intends to contact substance with the aberrant receptor. Furthermore, claim 52 also recites “substance as said receptor”, clearly a typographical error.

Claim 57 recites “Trp64Arg variant”, without indicating what Trp64Arg is a variant of, or from what organism (human, mouse, etc) this protein is isolated. Without a

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specific receptor or SEQ ID NO recited it is unclear what variant protein is claimed as applicant's invention.

Claims 53-56 are included in this rejection as depending from indefinite claims 45-48.

Applicant traverses this rejection on the grounds that "piecemeal examination should be avoided as much as possible" (page 5, paragraph 4, of Remarks, 17 January 2006). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. Piecemeal examination is to be avoided if possible. However, applicant has amended claims, cancelled claims and submitted new claims throughout the course of the extensive prosecution of this application thereby raising new issues which must be addressed. Additionally, applicant notes that new claims 45-54 are identical to claims 1-10 as issued in corresponding European Patent (EP 0 974 052 B1). However, EPO practice has no bearing on U.S. examination.

### ***35 U.S.C. § 112, First Paragraph***

Claims 45, 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 45 is broadly drawn to a method of screening for a substance "capable of operating an aberrant receptor" wherein the receptor contains a mutation resulting in substantially changed affinity for the natural ligand". Claims 55-57 recite the limitations of wherein the aberrant receptor is an adrenergic receptor (Claim 55), a  $\beta 3$  adrenergic receptor (Claim 56) and a Trp64Arg variant of the  $\beta 3$  adrenergic receptor (Claim 57). Pietri-Rouxel et al (1997, Eur J Biochem, 247:1174-1179) teach that the affinity of the [Arg64] $\beta 3$ -adenoreceptor for CGP 12177A, a specific  $\beta 3$ -adrenoceptor agonist, was

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indistinguishable from that of the wild-type receptor (page 1176, column 1, 1<sup>st</sup> paragraph, and page 1175, Table 1). Since the art of record teaches away from the limitations recited in the preamble of Claim 45, the artisan would not be able to make or use this method as recited by the claims of the instant invention.

### **35 U.S.C. § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45-54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Birnbaumer et al. (Mol Endocrinology 8:886-894, cited in previous Office Actions, the last being 17 October 2005) for reasons of record and those set forth below.

The instant invention reads on method steps for screening compounds.

Claim 45 recites the method steps of (a) expressing an aberrant genetic product by gene engineering technology; (b) bringing the aberrant receptor into contact with a test substance; and (c) assaying the "operation activity" of substance on receptor. Claim 46 recites the limitation that the substance be an agonist or antagonist to the receptor; Claim 47 recites assaying activity of said substance wherein the activity is an activity that restores the normal function of the cell. Claims 48-50 recite preparation of test substance and assaying the test substance in a cell expressing the gene encoding the aberrant receptor. Claim 51 recites the further limitation of that the aberrant receptor is one encoded by a gene from a cell of a mammal suffering from a disease caused by the aberrant receptor. Claim 52 recites the limitation of contacting isolated receptor with a test substance; claim 53 is drawn to a substance the "operates" the receptor; and claim 54 recites the limitation of the "operation activity" being a change in intracellular concentration of cAMP.



Birnbaumer et al. teach transfection of cells with cDNA encoding for the Q3 mutant receptor, a mutation of the type-2 vasopressin receptor. This receptor has been identified as present in cells of individuals suffering from a form of X-linked congenital nephrogenic diabetes insipidus (page 892, column 2, paragraphs 2-5). The mutated receptor has a 20-fold reduced affinity for arginine vasopressin (AVP) and stimulates adenylyl cyclase with an EC50 that is increased by a factor of 60-fold (page 886, abstract). The reference teaches that treating cells expressing mutant receptors with increasing concentrations of dDAVP (up to  $10^{-4}$  M), a V2R-selective agonist, results in adenylyl cyclase activity similar to that seen when the cells expressing wild-type receptor are treated with  $10^{-9}$  M dDAVP, (Figure 7, page 892). Thus, Birnbaumer et al. teach all the limitations of claims 45-54.

Claims 45-54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Green et al. (1993, J Biol Chem 31:23116-23121, cited in previous Office Actions, the last being 17 October 2005) for reasons of record and those set forth below.

The instant invention reads on method steps for screening compounds. Green et al. teach a mutant  $\beta_2$ -adrenergic receptor ( $\beta_2$ -AR) with impaired binding ability (about a 3.5-fold decrease in  $K_i$ ) for its natural ligand, epinephrine (Page 23116, Abstract), thus teaching a receptor with substantially changed affinity for natural substances. The reference compares the effects of incubating membranes from cells expressing wild-type and mutant  $\beta_2$ -AR with various concentrations of epinephrine on stimulation of adenylyl cyclase activity. Green et al. teach the basic method steps disclosed in the instant invention comprising bringing aberrant and normal receptors into contact with a substance (increasing concentrations of epinephrine) and determining and comparing the operation activity (adenylyl cyclase activity) of the two receptors. Thus, Green et al. teach all the limitations of claims 45- 54.

Claims 45-51 and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kong et al. (1993, J Biol Chem 31:23055-23056, cited in previous Office Actions, the last being 17 October 2005) for reasons of record and those set forth below.

The instant invention reads on method steps for screening compounds. Kong et al. teach a mutant  $\sigma$  opioid receptor which has reduced affinity for  $\sigma$  receptor-selective agonists (Page 23055, Abstract and page 23056, Figure 1 and page 23057, Figure 3 and Table 1). The binding of radioactive ligand was reduced approximately 75% compared to the wild-type receptor (page 23056, column 1, paragraph 3) thus teaching a receptor with substantially changed affinity for natural substances. The authors teach a "screening assay" in which COS-7 cells stably express both the wild-type and mutant receptors (page 23056, column 1, paragraph 3) are treated with a number of different opioid agonists and antagonists. Kong et al. compare inhibition of forskolin-stimulated cAMP formation in COS cells expressing the wild-type and mutant  $\sigma$  receptor incubated with a panel of opioid agonists (page 23056, Figure 2). Thus, this reference teaches the method steps of comparing the activity of a mutant receptor to that of a wild-type receptor when challenged with a "screening panel" of agonists and meets the limitations of the basic method steps disclosed in the claimed invention. Therefore, Green et al. teach all the limitations of claims 45-51 and 54.

Claims 45-57 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pietri-Rouxel et al. (1997, Eur J. Biochem 247:1174-1179). Pietri-Rouxel et al teach the expression of wild-type and [Arg64]  $\beta_3$  adrenergic receptor in CHO-K1 cells (page 1175, column 2, last paragraph). The cells were treated with CGP 12177A, a specific  $\beta_3$ -adrenoceptor agonist, and the adenylyl cyclase activity for CHO-K1/wild type and CHO-K1/[Arg64]  $\beta_3$  adrenergic receptor was measured (page 1176, column 2, and Figure 2, page 1177). Thus the teachings of Pietri-Rouxel et al. anticipate all the limitations of claims 45, and 55-57.

The recitation of "a method of screening for a substance capable of operating an aberrant receptor being a receptor with a mutation in the structural gene resulting in substantially changed affinity for the natural ligand" is in the preamble of claim 45. Moreover, the Art teaches that the mutation recited in the claims as the preferred embodiment, the Trp64Arg variant, does not meet the limitations of "a mutation in the structural gene resulting in substantially changed affinity for the natural ligand" (see

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discussion above), and therefore the preamble is given minimal patentable weight. The claims of the instant invention are all directed to method steps comprising: 1. expressing an aberrant genetic product by gene engineering technology; 2. bringing the aberrant receptor obtained in (1) into contact with a test substance; and 3. assaying the operation of said substance on said receptor. The working examples cited by the Applicant in response of 17 January 2006, (page 8, 1<sup>st</sup> paragraph) disclose a screening method (Example 7, paragraph 0147) in accordance with method of Example 6 (paragraph 0142). Example 6 teaches a method of determining ligand binding activity using CHO cells having the Trp64Arg variant, preparing a cell membrane fraction, and mixing this preparation with a test compound. The method steps recited in Example 6 are similar to those taught by Pietri-Rouxel et al.

Any study that teaches method steps of expressing a mutant receptor and assaying the functioning of that receptor in response to test compounds would meet the definitions of a screening assay as disclosed by the claims of the instant invention.

### **35 U.S.C. § 103(a)**

The rejections of claims 18, 19, 22, 23, 28-33, and 35-44 under 35 U.S.C. § 103(a) as being unpatentable over Lebrun et al in view of Choong et al., and further in view of Dower et al., all previously of record (cited in previous Office Actions, the last being 17 October 2005), are maintained for reasons of record in the previous Office Actions and are now applied to claims 45-53 of the instant invention.

Applicant traverses this rejection in reply of 10 January 2006 on the grounds that the instant claims are directed to methods of screening for a substance capable of operating an aberrant receptor with substantially changed affinity for the natural ligand and that Lebrun et al. does not teach mutant receptors having substantially changed

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affinity for their natural substrate (page 9, 1<sup>st</sup> paragraph). Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons.

The instant invention reads on method steps for screening compounds. The references cited by the examiner, Lebrun et al and Choong et al., teach *in vitro* systems for studying the functioning of mutated receptors compared to their wild-type counterparts. Thus they all teach method steps comprising "expressing an aberrant genetic product by gene engineering technology", bringing an "aberrant receptor into contact with a subject substance", "assaying the operation activity of said substance on said receptor". Lebrun et al. differ from the claims in that the receptor mutation was not in the ligand binding domain of the receptor. Choong et al. teach a disease in which partial androgen insensitivity was shown to be due to a mutation in the ligand-binding domain of the androgen receptor (AR) gene. It would have been obvious to the person of ordinary skill in the art at the time of instant invention to substitute the mutated AR of Choong et al. in the method of Lebrun et al. for the purpose of finding of a substance that would compensate for the AR mutation described by Choong et al. One of ordinary skill in the art would have been motivated to use the screening method of Lebrun et al., with a receptor that had a mutation that affected ligand binding, since one of ordinary skill in the art would want to screen for drugs that could be used to therapeutically treat individuals that had such a mutant receptor. The art recognizes how common mutations in the ligand-binding domain of receptors are, and that such mutant receptors could be used to screen for compounds that would bind and activate them. Dower et al. is cited to show that it was well-known in the art at the time of the invention that many types of compounds could be screened for therapeutic purposes and these compounds could be utilized to produce a useful, functional activity. Thus, one of ordinary skill in the art at the time of the invention would have been motivated to use the screening methods of Dower et al., in which large numbers of chemically synthesized molecules and natural products could be screened in the receptor assays cited in Lebrun et al., and Choong et al. to identify compounds that could activate the mutant receptor (which did not respond to the cognate ligand) in order to search for compounds in the development of new pharmaceutical agents. One of ordinary skill in the art at the time

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of the invention would have a reasonable expectation of success since screening combinatorial libraries for therapeutic compounds had been used extensively in the pharmaceutical industry.

Applicant asserts that "Lebrun et al. does not teach any 'screening assays' as this term is understood in the context of the pending claims.....Lebrun et al. was a purely mechanistic study, and not a screening assay for compounds....." (page 9, last paragraph, bridging page 10). Applicant's assertions have been fully considered but they are not deemed to be persuasive. As previously discussed (see, for example, Office Action of 17 October 2005) any assay which recites method steps involving examining the response of a mutant receptor in the presence of a test compound could be interpreted as a screening assay. Determining the function of a mutant receptor following incubation with a given compound or set of compounds would constitute the outlines of a screening assay, even if it is not specifically taught as such.

**Conclusion:**

No claims are allowed.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
**LORRAINE SPECTOR**  
**PRIMARY EXAMINER**